

Novel Antihistamines

Pankaj Gupta*, Ujala Verma, Rashmi Sharma

Histamine (H_1) receptor antagonists are one of the commonly used drugs. The second generation histamine H_1 receptor antagonists, the so called 'non sedating' antihistamines, have high potency and additional antiallergic properties. In fact these have replaced the older drugs because they lack sedation and cardiovascular side effects.

Ebastine (1,2) is an effective non sedating H_1 receptor antagonist marketed for the treatment of allergic rhinitis and urticaria. After oral administration it is extensively and rapidly metabolized to its active metabolite, carebastine. After ingestion of ebastine 10mg, the carebastine C_{max} of 120 μ g/litre is obtained in 3-6 hours. Bioavailability is good and food ingestion seems to increase the bioavailability. Carebastine has V_d (volume of distribution) of 90-143 litre and 98% plasma protein bound (PPB). In hepatic or renal dysfunction its dose adjustment may not be necessary. Moreover, it does not appear to interact with alcohol (ethanol), diazepam or cimetidine. A significant increase in plasma carebastine concentration may occur when ketoconazole 400mg/day or erythromycin 500mg 6 hourly are concomitantly administered with ebastine. It has a dose related suppressive effect on histamine induced wheals and flares over the dose range of 3-30 mg. After a single dose, the maximum suppressive effect occurs at 6-8 hours. After a short course of ebastine, the residual effect lasts for 3-4 days. Tachyphylaxis to ebastine has not been reported.

Levocabastine (1) has a terminal $t_{1/2\beta}$ of 35-40 hours and is only available as a topical application administered intranasally or ophthalmically in patients with rhinoconjunctivitis. Absorption from nasal or ophthalmic formulations occur within 1-2 hours. Steady state plasma concentration achieved in 7-10 days are approximately 10.5 μ g/litre after 2 nasal sprays (50 μ g/spray) per nostril

three times daily and 1.6 μ g/litre after application of 0.05% ophthalmic suspension, 1 drop (15 μ g) per eye three times daily. Oral and intravenous formulations are not used clinically because of potential sedative effects. Sixty to seventy percent of it is excreted unchanged in urine and 10-20% appears unchanged in faeces because of biliary excretion. After single or repeated doses the $t_{1/2\beta}$ of levocabastine is between 35-40 hours regardless of the route of administration.

Mizolastine (1,3,4), another second generation antihistaminic is a potent and selective H_1 receptor antagonist lacking affinity for H_2 , H_3 , muscarinic and serotonergic receptors. In addition at usual clinical doses it inhibits neutrophil migration, mast-cell histamine release and the activity of 5-lipoxygenase in animal models. The anti 5-lipoxygenase activity might explain the inhibition of the arachidonic acid induced cutaneous inflammatory reactions by mizolastine. After oral administration, it is rapidly absorbed with a mean peak plasma concentration (C_{max}) of 276 μ g/litre. Bioavailability is 65.5% and is not affected by age or concomitant ingestion of food or alcohol. It has V_d of 1.4 litre/kg with 98.4% PPB. It is extensively metabolized by glucuronidation with less than 0.5% of the administered dose excreted unchanged in urine. Clinical studies have demonstrated lack of diffusion into the CNS, lack of anticholinergic activity, the rapidity of onset and prolonged duration of action allowing once daily administration. Its $t_{1/2\beta}$ is prolonged (but within the normal range) by 47% in patients with renal disease and no dose adjustment is required. It has no effect on pharmacokinetics of theophylline, digoxin, R-(+)- and S-(-)-warfarin or diltiazem. Mizolastine 10mg suppresses histamine induced wheals and flares significantly within 1 hour of administration. Peak effect occurs in 3-12 hours and suppression lasts for 24 hours. It also produces dose

From The P.G Department of Pharmacology & Therapeutics, Govt. Medical College Jammu and *ENT, Govt. District Hospital, Jammu.
Correspondence to: Dr Pankaj Gupta, House No. 12, Tara Vihar, Paloura, Jammu (J&K).

related bronchodilation and protection against histamine induced broncho-constriction. Tachyphylaxis to mizolastine has not been reported. The suppressive effect of mizolastine on wheals and flares induced by histamine, codeine or allergen remains highly significant even after 3 months of regular administration.

Levocetirizine (5-7), a new, once-daily, nonsedating antihistamine is the active enantiomer of cetirizine, a potent histamine H₁-receptor antagonist. Cetirizine is a racemic mixture of levocetirizine and dextrocetirizine. Recent data has demonstrated that the antihistaminergic activity of the racemate is primarily due to levocetirizine. Levocetirizine is rapidly and extensively absorbed, poorly metabolized, and not subject to racemization. Its apparent V_d is smaller than that of dextrocetirizine (0.41 litre/kg vs. 0.60 litre/kg. Moreover, the non-renal (mostly hepatic) clearance of levocetirizine is also significantly lower than that of dextrocetirizine (11.8 mL/ min vs. 29.2 mL/ min). Levocetirizine has been found to be equally effective as desloratidine and fexofenadine in attenuating the response to nasal adenosine monophosphate (AMP) challenge as well as in an nasal provocation test (NPT) with grass pollen allergen. In the comparative trials in patients with seasonal allergic rhinitis, 5 mg levocetirizine has been found to be equivalent to 10 mg cetirizine.

Desloratidine (8), a new H₁receptor antagonist, is the primary active metabolite of loratidine. Early studies have demonstrated that desloratidine is approximately 10–20 times more potent in H₁ receptor binding than loratidine in vitro and has 2.5-4 times more antihistaminic potency in animals. In clinical trials with desloratidine, there were no clinically relevant changes in cardiac conduction at doses upto 9 times the recommended clinical doses.

Fexofenadine (1) is the active metabolite of terfenadine. It is readily absorbed after oral administration, with t_{max} of 1 to 3 hours. Absorption is not affected by food and about 70% PPB. It gets primarily eliminated unchanged in faeces and urine and has a terminal half life t_{1/2β} of ~14 hours and duration of action of 24 hours making it suitable for once or twice daily administration. Tachyphylaxis to fexofenadine has not been observed.

Olopatadine (9), is an agent that exerts both a mast cell stabilization effect and an anti histaminic effect. In a controlled double blind study, topical olopatadine 0.05%

and 0.1% solutions assessed in patients with allergic conjunctivitis using conjunctival allergen challenge model to determine efficacy. Both concentrations were significantly better than placebo in alleviating itching and redness in test subjects. It was effective if administered within 30 minutes of allergen challenge and was effective for upto 8 hours. The fact that it displayed a low affinity for 38 nonhistamine receptor binding sites suggests that it will have few adverse effects. It thus appears to be a promising new agent for the treatment of ocular allergy. Other interesting future therapeutic possibilities include single chemical entities with clinically relevant intrinsic dual pharmacological activity for example combined H₁ and H₂ antagonism, H₁ antagonism and cystinyl leukotriene antagonist activity or H₁ antagonism and 5-lipoxygenase activity. Introduction of these novel therapeutic strategies would be a therapeutic miracle of the new millenium.

References

1. Simons FER and Simons KJ. Clinical pharmacology of new histamine H₁ receptor antagonists. *Clin pharmacokinet* 1999; 36(5): 329-52.
2. Horak F and Stubner UP. Comparative tolerability of second generation antihistamines. *Drug Saf* 1999; 20(5): 385-401.
3. Lebrun-Vignes B, Diquet B, Chosidow O. Clinical pharmacokinetics of mizolastine. *Clin Pharmacokinet* 2001; 40(7): 501-07.
4. Dubertret L, Pecquet C, Murrieta-Agultes M, Leynadier F. Mizolastine in primary acquired cold urticaria. *J Am Acad Dermatol* 2003; 48: 578-83.
5. Tillement JP, Testa B, Bree F. Compared pharmacological characteristics in humans of racemic cetirizine and levocetirizine, two histamine H₁-receptor antagonists. *Biochem Pharmacol* 2003; 66(7): 1123-26.
6. Lee DK, Gardiner M, Haggart K, Fujihara S, Lipworth BJ. Comparative effects of desloratadine, fexofenadine, and levocetirizine on nasal adenosine monophosphate challenge in patients with perennial allergic rhinitis. *Clin Exp Allergy* 2004; 34(4): 650-53.
7. Deruaz C, Leimgruber A, Berney M, Pradervand E, Spertini F. Levocetirizine better protects than desloratadine in a nasal provocation with allergen. *J Allergy Clin Immunol* 2004; 113(4): 669-76.
8. Monroe E, Finn A, Patel P *et al.* Efficacy and safety of desloratadine 5mg once daily in the treatment of chronic idiopathic urticaria: A double blind randomized, placebo controlled trial. *J Am Acad Dermatol* 2003; 48: 535-41.
9. Olopatadine. www.medformation.com/ac/mm_usp.nsf/usp/203483b.htm. Accessed on 17th Sept. 2005.